

## Insidious progressive bone destruction in a dog surgically treated for otitis media: follow-up by clinical examination and computed tomography

*Progressieve botdestructie bij een hond die operatief werd behandeld voor otitis media: follow-up via klinisch onderzoek en computertomografie*

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## ABSTRACT

A 5.5-year-old Beagle was evaluated for abnormal swallowing and a head tilt of a two-weeks duration. Inspection of the throat and external ear canal revealed an intact but abnormally bulging eardrum. Computed tomographic (CT) examination showed a right-sided tympanic bulla filled with soft-tissue density material, a partially lytic ventral wall and lysis of the petrosal part of the temporal bone. Through ventral bulla osteotomy, sterile cholesterol granuloma and cholesteatoma were diagnosed. The dog recovered but the head tilt re-appeared eight months after surgery. A new CT scan showed expanded lysis of the tympanic wall and increased bone lysis within the petrosal portion of the temporal bone. The owner elected for no further treatment. Another two years later, a third CT scan was performed. Prominent intracranial involvement was present. In contrast to the extent and the progression of the changes, the dog was clinically stable.

## SAMENVATTING

Een beagle van 5,5 jaar oud werd aangeboden omwille van klachten van abnormaal slikken en een scheve kopstand die reeds twee weken aanwezig was. Inspectie van de keel werd uitgevoerd. Op otoscopisch onderzoek werd een intact maar bolstaand trommelvlies aangetroffen. Op de beelden van het computertomografisch (CT) onderzoek bleek de rechter bulla tympanica gevuld met materiaal met een weke-delendensiteit, terwijl de ventrale bullawand deels lytisch was, evenals het pars petrosa van het os temporale. De bulla werd benaderd via ventrale bulla osteotomie, waarbij een steriel cholesterol granuloom en een cholesteatoma werden gediagnosticeerd. De hond herstelde, maar acht maanden na de chirurgie trad opnieuw een scheve kopstand op. Een nieuwe CT-scan toonde uitbreiding van de lyse van de bullawand en toegenomen lyse van het pars petrosus van het os temporale aan. De eigenaar wenste geen nieuwe chirurgische interventie. Nog eens twee jaar later, werd de CT-scan herhaald. Ditmaal was er een duidelijke intracraniale uitbreiding van het letsel zichtbaar. Niettegenstaande de uitgebreidheid en de progressie van de letsels was de hond klinisch stabiel.

## INTRODUCTION

In dogs, the prevalence of otitis media secondary to otitis externa is relatively high. Nevertheless, many cases are overlooked since the historical presentation of chronic middle ear disease mimics the clinical signs

of therapy-resistant otitis externa (Gotthelf, 2004). Both cholesterol granuloma (Fliegner et al., 2007) and cholesteatoma (Lidl et al., 1991) can occur in complicated otitis media cases in dogs. A cholesterol granuloma is a slow-growing, non-neoplastic lesion composed of cholesterol clefts surrounded by

granulation tissue, macrophages and foreign body giant cells (Cox and Payne-Johnson, 1995; Banco et al., 2014). There are only three cases reporting the presence of a clinically relevant cholesterol granuloma in the tympanic bulla in a dog (Cox and Payne-Johnson, 1995; Fliegner et al., 2007; Riedinger et al., 2012). In contrast, middle ear cholesteatoma seems more common in dogs (Little et al., 1991; Hardie et al., 2008; Greci et al., 2011). However, this condition is probably also underdiagnosed. Cholesteatoma is characterized by the presence of metabolically active squamous epithelium surrounding lamellar sheets of keratin debris (Little et al., 1991; Banco et al., 2014). In a study on inflammatory middle ear disease in dogs, cholesteatoma was diagnosed in as many as 11 % of the affected ears (Little et al., 1991).

The symptoms observed in dogs affected by cholesterol granuloma or cholesteatoma depend on the affected structures. Pain upon palpation of the bulla or the temporomandibular joint and upon opening of the mouth are symptoms, which are very frequently observed in dogs with cholesteatoma (Greci et al., 2011). Discomfort upon opening of the mouth was also reported in two of the three cases of canine middle ear cholesterol granuloma (Fliegner et al., 2007; Riedinger et al., 2012). Also neurological complaints, such as head tilt, facial paralysis and ataxia are common in dogs with cholesteatoma (Little et al., 1991; Hardie et al., 2008). In only one of the three cases reporting a dog with cholesterol granuloma, occasional and momentary facial palsy and head tilt were reported by the owner, although neurological examination at the time of presentation to the veterinarian was unremarkable (Riedinger et al., 2012).

Owing to its ability to detect subtle bony changes, computed tomographic (CT) scanning is considered the best imaging technique to identify cholesteatoma in human patients who had not already had surgery (Williams et al., 2003; De Foer et al., 2007). Also in dogs, the CT finding of an expansile tympanic cavity mass is highly suggestive for cholesteatoma (Hardie et al., 2008; Travetti et al., 2010). There is recent evidence that middle ear cholesterol granuloma in dogs may also induce bone lysis (Fliegner et al., 2007; Riedinger et al., 2012). In humans, magnetic resonance imaging (MRI) is used for the differentiation between aural cholesteatoma and cholesterol granuloma, based on the difference in signal intensity on T1-weighted images (Muzumdar et al., 2002). In dogs, MRI findings have been described in one case of cholesterol granuloma only (Riedinger et al., 2012). In two case series on cholesteatoma in dogs, the use of MRI has been reported (Sturges et al., 2006; Hardie et al., 2008), but only recently, the MRI features in three dogs with aural cholesteatoma have been described (Harran et al., 2012; Schuenemann and Oechtering, 2012).

Medical therapy is not a viable treatment in humans with cholesteatoma or cholesterol granuloma

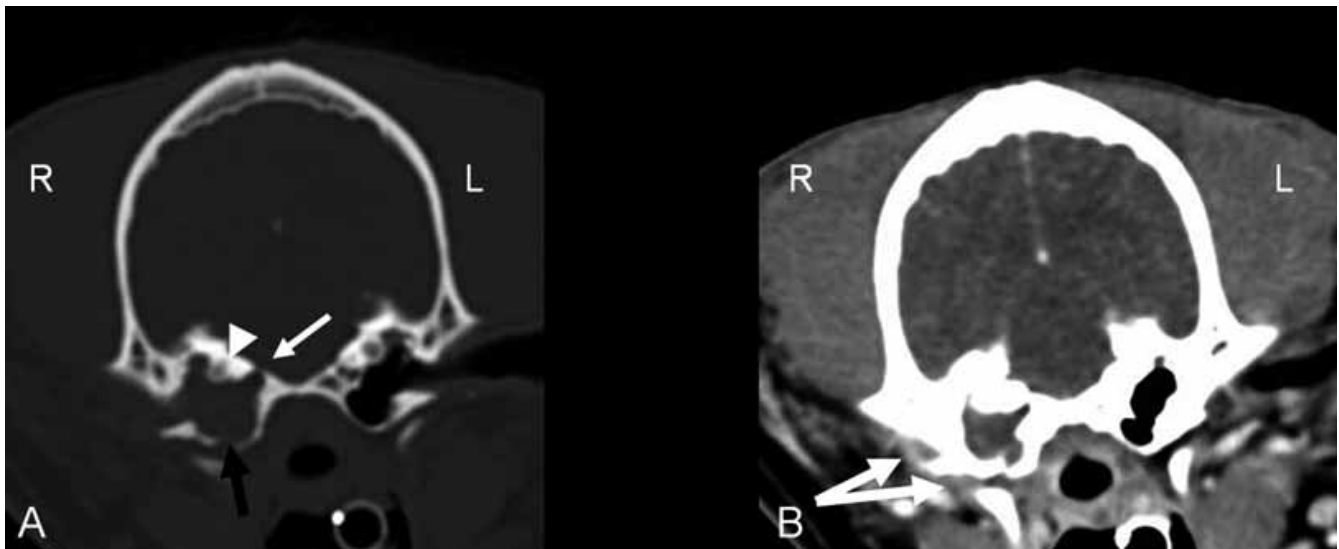
because expansion in close proximity to the ear is potentially dangerous. However, following surgery, a cholesteatoma persistence or recurrence rate as high as 50% has been reported (Ajalloueyan, 2006). Therefore, affected patients are routinely submitted to regular follow-up checks to allow early detection of recurrence (Roland, 2014). However, CT as well as MRI seem to show a limited sensitivity in the postoperative patient to diagnose recurrent disease (Williams et al., 2003; Vercruysse et al., 2006). Also in dogs, the only treatment for cholesteatoma is the surgical removal of the entire epithelium (Hardie et al., 2008). In veterinary patients, an intensive follow-up is greatly lacking, and repeated scans are mostly preserved for symptomatic patients only. Recurrence is observed in 25 to 50% of the dogs diagnosed with cholesteatoma (Little et al., 1991; Hardie et al., 2008; Travetti et al., 2010; Greci et al., 2011).

The dog of the present case showed insidious progressive bone destruction on repeated CT examinations after surgical removal of a middle ear cholesterol granuloma and cholesteatoma in the absence of deterioration of the clinical signs.

## CASE PRESENTATION

A 5.5-year old, female, intact Beagle was brought to the referring veterinarian for a head tilt towards the right. Two weeks previously, the owners had noticed a sudden onset of abnormal swallowing and a raucous coughing. The dog's previous medical history was unremarkable. General anesthesia was induced to facilitate the inspection of the nasopharynx and both ears. The eardrum was opaque and bulging into the external ear. Following unsuccessful initial conservative management with amoxicillin and clavulanic acid (Synulox<sup>®</sup>, Pfizer Animal Health BV, Puurs, Belgium, 12.5 mg/kg, PO, q 12 h) in combination with enrofloxacin (Baytril<sup>®</sup>, Bayer, Diegem, Belgium, 5 mg/kg, PO, q 24 h), the dog was referred to the Faculty of Veterinary Medicine of Ghent University for a CT scan of the skull.

Both native and contrast (Omnipaque<sup>®</sup> Nycomed, Brussels, Belgium, 300 mg I/ml, in a dosage of 1.5 ml/kg, IV, CT examinations were performed. A single row detector spiral CT (Prospect, GE Medical Systems, Milwaukee, WI) was used with tube voltage 120 KvP and 100 mAs. Contiguous slices were made from the first cervical vertebra to the cribriform plate, perpendicular to the hard palate. Slice thickness was 3 mm, and a bone algorithm was used during survey CT and standard algorithm during contrast CT. To reduce partial volume artefacts, the region of interest was re-scanned in 1mm thick slices. 2D multiplanar reconstructed images were made in dorsal and sagittal planes. In the initial studies, the right-sided tympanic bulla appeared to be filled with soft-tissue density material and showed a partially lytic ventral wall (Figure 1). The bulla tympanica showed an abnormal

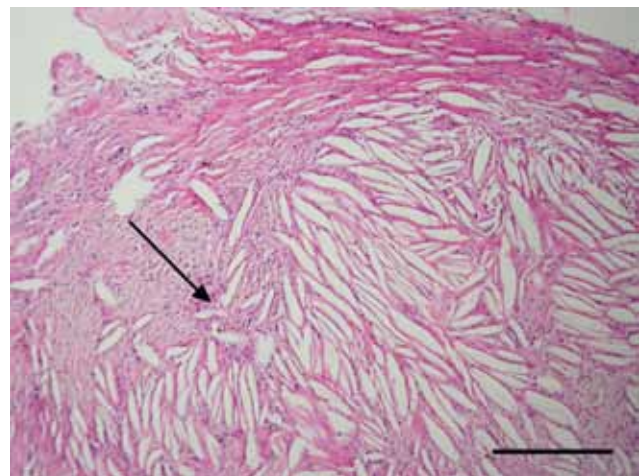


**Figure 1.** Transverse CT pre-contrast image in bone window (A) and post-contrast image in soft tissue window (B) before surgery show an enlarged shape of the right bulla and filling with soft-tissue density material. Partial destruction of the ossicles (white arrowhead) and lysis at the ventral wall of the bulla can be noticed on the bone window image (black arrow). A focal area of bone destruction is present at the petrosal portion of the temporal bone (white arrow). The white arrows on the post-contrast image indicate enhancement of the soft tissues ventrally of the bulla.

and enlarged shape. A focal area of bone destruction was present at the petrosal portion of the temporal bone. The ossicles were partially destroyed. The soft-tissue mass extended at the level of the malleolus and an external bulging of the tympanic membrane was present. No abnormalities at the external ear canal were present. In the contrast study, no abnormal contrast medium enhancement could be noticed intracranially or within the bulla, although there was mild enhancement in the soft tissues ventral to it. Based on the CT scan, the differential diagnosis was isolated otitis media or otitis media and interna, most likely due to cholesteatoma.

The dog was referred to the surgical department of Small Animal Medicine of the Faculty of Veterinary Medicine, Ghent University and scheduled for a unilateral ventral bulla osteotomy (VBO). The ventral wall of the bulla was grossly osteolytic and destroyed, and a sample was submitted for bacteriological aerobic and anaerobic culture. A solitary 5x5x5 mm brown nodule was visualized in the tympanic cavity as well as a large amount of white pasty substance. Both were removed and fixed separately in 10% formalin for histopathological evaluation. After gentle curettage, the tympanic cavity appeared to be empty and the surgical site was copiously lavaged with warm sterile saline and closed routinely.

The morning after surgery, the dog showed a discrete facial nerve weakness with slow palpebral reflex and drooping of the ipsilateral eyelid but appeared comfortable, ate and was discharged from the hospital. Medications were prescribed, including the antibiotics amoxicillin and clavulanic acid (12.5 mg/kg, PO, q 12 h) and enrofloxacin (10.0 mg/kg, PO, q 24 h) and a NSAID (meloxicam 0.1 mg/kg, PO,

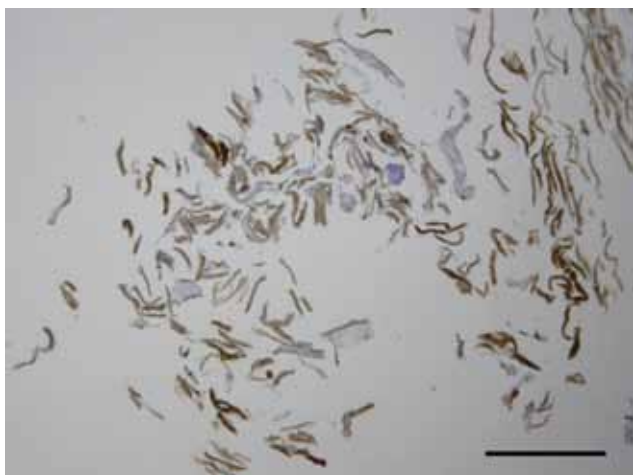


**Figure 2.** Cholesterol granuloma, fusiform clefts (arrow) left by cholesterol crystals, which have been dissolved during processing. H&E, 100x. Bar = 20  $\mu$ m.

q 24 h) for five days. The cornea was protected by regular application of synthetic tears.

Bacterial culturing of the intraoperative samples yielded no growth and both of the antibiotics were discontinued. The biopsy samples were processed routinely and stained with HE. On microscopy, the slides of the round, brown nodule contained large numbers of acicular clefts, typical of cholesterol crystals surrounded by mononuclear inflammatory cells (mostly macrophages), giant cells and some fibroblasts (Figure 2). Cholesterol granuloma was diagnosed. The samples of the pasty material showed broad acellular fibres on microscopic examination. These were keratin fibres, confirmed by positive cytokeratin staining (Figure 3). None of the submitted





**Figure 3. Acellular keratinous material. Cytokeratin stain, 200x. Bar = 20 µm.**

samples contained epithelium. Nevertheless, the presumptive diagnosis of cholesteatoma was made.

The dog's clinical signs fully resolved within the next two weeks. However, a head tilt towards the right re-appeared eight months postoperatively. The referring veterinarian diagnosed bilateral *Malassezia otitis* and instituted a topical treatment with nystatin-neomycin triamcinolone acetonide ointment once daily for two weeks. The head tilt did not alter by this treatment and a re-examination CT scan was scheduled nine months after VBO surgery, using the same imaging protocol as before. Slight extension of soft-tissue material in the distal external ear canal and expanded lysis of the tympanic wall could be appreciated (Figure 4). Sequels of the VBO appeared present as the absence of a large part of the ventral and medial wall of the bulla. There was increased lysis of the petrosal part of the temporal bone, and

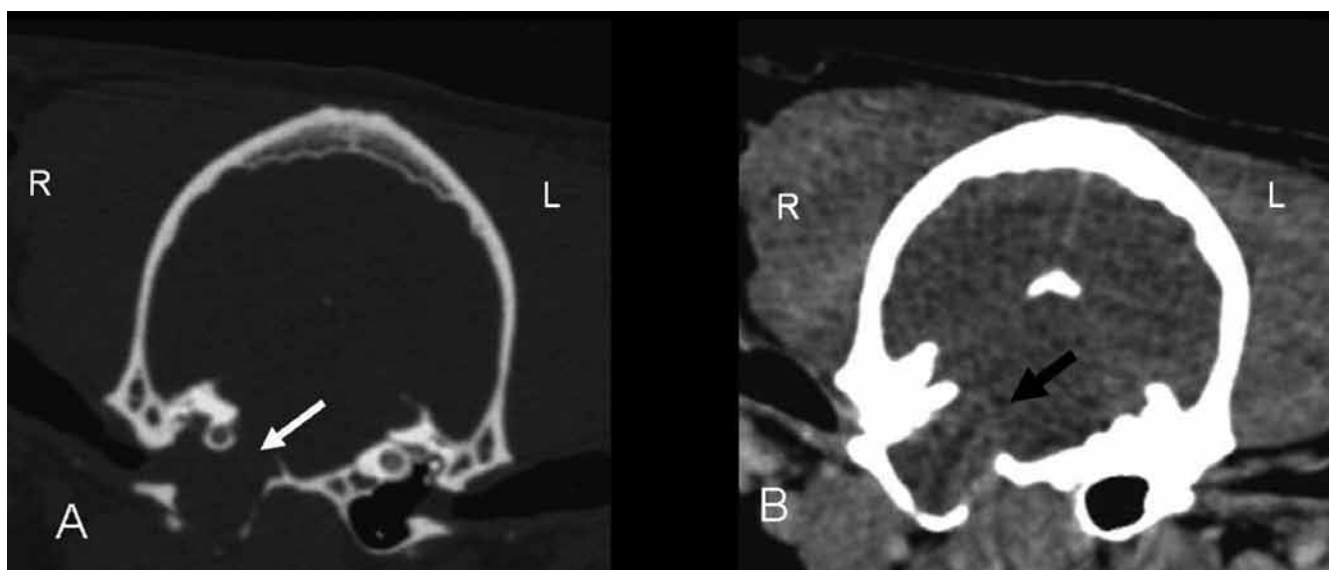
the ossicles seemed to be destroyed. The tympanic membrane seemed to be intact. The bulla was completely filled with a soft tissue attenuating mass slightly enhancing after IV contrast administration. Intravenous contrast showed rim enhancement of the soft-tissue mass extending intracranial at the level of the cerebellum. Because of the extension towards the brain, a new surgical approach carried an unjustified iatrogenic risk.

Two years after the second CT examination, i.e. 33 months after VBO surgery, the dog was represented at the authors' request to assess the progression of the bony destructive lesions and the expansion of the disease by a follow-up CT scan. There was a slight increase of lysis at the petrosal portion of the temporal bone compared to the previous study (Figure 5). Again, the soft tissue mass in the bulla enhanced mildly after IV injection of contrast medium. Moreover, the margins of the intracranial extension of the soft-tissue mass enhanced after IV contrast. Enhancement of the meninges as is encountered in case of meningitis, could not be noticed on the IV contrast images. In contrast to the extent and the progression of the changes seen on CT, the dog was clinically healthy apart from a discrete and stable residual head tilt. The owners declined further MRI examinations proposed to assess the intracranial extension of the lesion.

The dog was rechecked clinically and continued to have excellent clinical function 48 months after the VBO.

## DISCUSSION

An adult dog surgically treated for middle ear cholesterol granuloma and cholesteatoma was represented twice for follow-up CT scans. Progressive lesions were



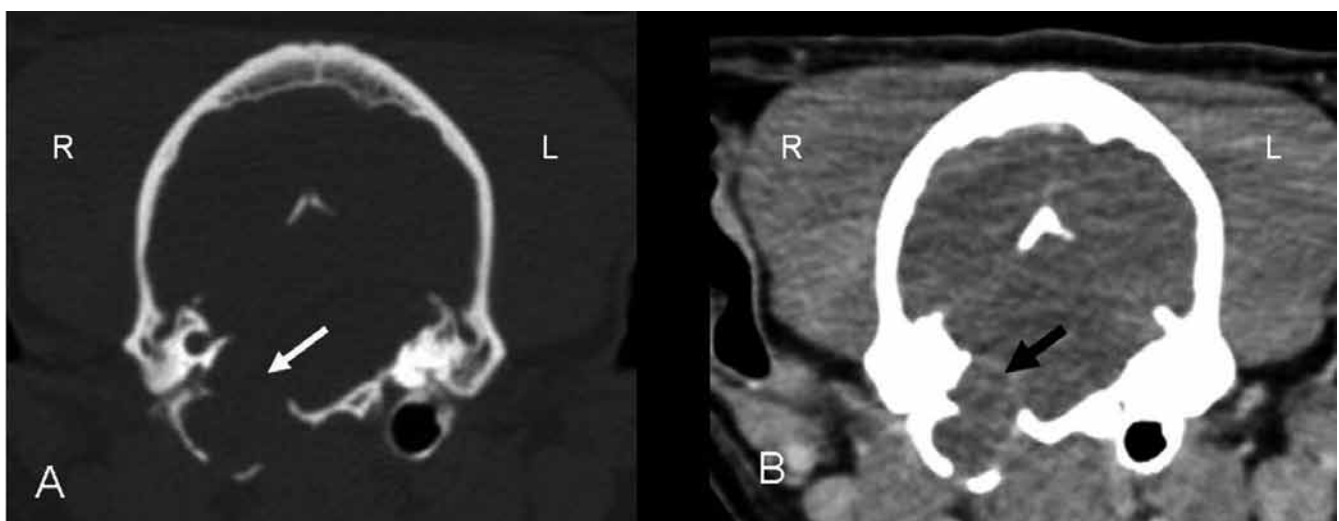
**Figure 4. The native CT study (A) nine months after surgery shows an increased lysis of the petrosal part of the temporal bone and the ossicles seem to be destroyed (white arrow). IV contrast (B) shows rim enhancement of the soft-tissue mass extending intracranially at the level of the cerebellum (black arrow).**

visible at both occasions and a prominent intracranial involvement was demonstrated, although the dog only had a mild and stable head tilt.

Computed tomographic scanning is a useful imaging modality for the detection and for the extension of middle ear pathologies and possible associated bony lysis in dogs (Love et al., 1995; Rohleder et al., 2006; Travetti et al., 2010). It provides excellent anatomical detail and the relationship between the mass and contiguous structures, allowing a better treatment and prognosis. Evaluating the images on bone window and soft-tissue window is necessary to define the complete extension. The use of small CT slice thickness decreases the incidence of partial volume artefacts, which occur in the tympanic region of companion animals (Barthez et al., 1996; Garosi et al., 2003). According to a relatively recent report on CT features in dogs affected by cholesteatoma, there is no appreciable contrast medium enhancement in the tympanic bulla, although occasionally, ring enhancement can be appreciated (Travetti et al. 2010). However, in another report, heterogenous contrast medium enhancement was observed in the majority of the patients. It was interpreted as increased vascularity in the abnormal metabolically active squamous epithelium, surrounding the keratin debris (Hardie et al., 2008). The appreciated changes, such as a lytic bulla, a soft tissue-like opacity in the bulla and a sclerotic or lytic aspect of the petrosal portion of the temporal bone are amongst the clinical features of cases of aural cholesteatoma (Hardie et al., 2008; Travetti et al., 2010) but potentially also of aural cholesterol granuloma (Fliegner et al., 2007; Riedinger et al., 2012). The final diagnosis and differentiation between cholesterol granuloma and cholesteatoma can only be made by histopathologic evaluation of the middle ear contents. In the present case, a firm nodule (cholesterol granuloma) was removed as well

as pasty substance (no discrete mass) that was readily encountered after entering the bulla (keratin debris). Also four dogs in a previous case series of eleven cholesteatoma patients demonstrated the contemporary presence of cholesteatoma and multiple cholesterol granulomas (Banco et al., 2014). The cholesterol clefts surrounded by granulation tissue are easily recognized as cholesterol granuloma (Cox and Payne-Johnson, 1995), whereas in the classical description of cholesteatoma, a keratinizing stratified squamous epithelium is shedding keratin into the lumen of a cyst (Little et al., 1991; Davidson et al., 1997). It is not unusual for human pathologists to receive middle ear samples obtained for histopathologic examination that only contain keratin. Notwithstanding the lack of epithelium, those cases are diagnosed as being 'compatible with cholesteatoma' since no apparent differential diagnosis exists (personal communication L. Stessens). Whereas the routine HE staining might be misleading, e.g. in case of the presence of fibrin after hemorrhage, immunohistochemistry (cytokeratin staining) confirms the presence of keratin. Also in the present case, a squamous epithelial lining could not be identified in the submitted samples. Very recently, it has been documented that the cytokine pattern of expression in epithelium obtained from within the tympanic bulla cannot be used as a histological feature to suggest the cholesteatoma origin of the middle ear pathology in dogs (Banco et al., 2014). On the other hand, epithelial hyperplasia in the absence of adnexa is highly suggestive of the presence of cholesteatoma (Banco et al., 2014).

After VBO, the tympanic cavity heals by ingrowth of granulation tissue and an obliterating proliferative bony response (Mc Anulty et al., 1995) or by a partial or complete bulla reformation (Holt and Walker, 1997). During the follow-up CT examinations in the present report, refilling of the bulla and progressive



**Figure 5.** The bone window CT image (A), two years and nine months after surgery present a slight increase of lysis at the petrosal portion of the temporal bone (white arrow). The wall of the intracranial extension (black arrow) of the soft-tissue mass enhances well after IV contrast (B).

bone resorption were appreciated. Soft-tissue opacity within the tympanic bulla may be attributable to the presence of fluid or soft tissue-like material, such as recurrent cholesteatoma, granulation tissue or fibrous scar tissue, or mucosal edema. Computed tomographic density measurements are of little use because the values of Hounsfield units are similar in all those conditions (Gotthelf, 2004). Nevertheless, this differentiation is important since the appropriate therapy may vary from supportive measures to follow-up surgery. Although antibiotic treatment is rarely effective in resolving recurrent middle ear infection after previous surgery (Smeak et al., 1996), controlling inflammation and infection by sustained antibiotic therapy might limit the clinical signs in dogs with recurrent cholesteatoma (Hardie et al., 2008). In the dog described, no medical treatment was installed in the later postoperative phase.

Several studies have evaluated the role of MRI in the differentiation of granulation tissue from recurrent cholesteatoma in human patients who had middle ear surgery. The use of delayed contrast-enhanced T1-weighted imaging is beneficial (Williams et al., 2003) in differentiating non-enhancing, avascular cholesteatoma from slowly enhancing inflammatory and scar tissue in postoperative recidivism. Differentiation is made based on the different enhancement patterns in relation to the time period after contrast administration. In one of the canine cases of cholesteatoma, in which the MRI findings have been described in detail, some partial enhancement of the inner lining of the bulla was observed on the post-contrast T1-weighted images (Harran et al., 2012). According to the authors, the enhancement following contrast administration suggest the presence of inflammation in conjunction with the presence of the cholesteatoma.

More recently, in a number of human reports, the value of diffusion-weighted (DW) MRI as an accurate method for the evaluation of intracranial disease processes has been discussed. The method has been shown to be accurate in differentiating inflammatory tissue from cholesteatoma in the non-surgically treated middle ear, as cholesteatoma demonstrates a clear hyperintensity on DW sequences in contrast to inflammatory tissue (Vercruysse et al., 2006; De Foer et al., 2007), especially when used in conjunction with standard MRI sequences (Vercruysse et al., 2006). In the dog reported here, with DW MRI, it would probably have been possible to accurately differentiate inflammatory tissue from cholesteatoma but the equipment is currently not available for veterinary use in Belgium. To the authors' best knowledge, the use of DW MRI to assess pathology of the middle ear has even not yet been described in animals.

It is very striking that the clinical condition of the dog of the present case was not deteriorating by the time of writing, more than four years after the surgery, notwithstanding the progressive destructive

lesions on the CT images. The progressive bone resorption did not only seem to affect the tympanic portion of the temporal bone but also the petrosal portion of the temporal bone, suggesting intracranial extension of the disease process. Surprisingly, symptoms compatible with intracranial involvement, such as central vestibular syndrome, abnormal gait, seizures, altered mentation or cranial nerve deficits (Sturges et al., 2006) were lacking in this dog and, moreover, chronic intermittent systemic antibiotic therapy was not required to keep the dog clinically stable. Previous studies on otogenic intracranial spread of middle ear infection showed obvious central disease in all affected dogs that arose from the space-occupying nature of the lesions and/or resulted from inflammation or edema of the brain parenchyma (Spangler and Dewey, 2000; Sturges et al., 2006). Also in humans, the potential for causing central nervous system complications makes cholesteatoma a potentially fatal lesion if infection is involved (Roland, 2014). In the case series of Hardie et al. (2008), there was one dog readmitted postoperatively with lysis of the petrosal portion of the temporal bone into the cranial fossa in the absence of signs of central neurologic disease. It is not clear why that particular dog as well as the dog described in this case report did not show more severe neurological symptoms despite the marked intracranial involvement.

In dogs with chronic middle ear disease, CT is a valuable modality to assess the presence of bony involvement. The contents of the tympanic bulla that is removed at the time of surgery, should be submitted for histopathological evaluation to differentiate between cholesterol granuloma, cholesteatoma, abscedation or neoplastic disease. Following surgery, it is not yet feasible in dogs to differentiate between recurrence and inflammatory or scar tissue formation. More cholesteatoma cases should have an extended follow-up, using CT or MRI to assess whether the dry keratin formed in cases of cholesteatoma (as long as it does not get secondarily infected) gives rise to less clinical signs than when a lot of inflammatory mediators are released.

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